Docket No.: PF-0066-2 DIV

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1642

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#17
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5-9-02

In re Application of: Janice Au-Young

Title: NOVEL HUMAN STEM CELL ANTIGENS

Serial No.: 09/225,080 Filing Date: January 4, 1999

Examiner: Canella, K. Group Art Unit: 1642

BOX AF
Commissioner for Patents
Washington, D.C. 20231

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal mailed October 31, 2001 and received in the Patent Office January 10, 2002, herewith are three copies of Appellants' Brief on Appeal. Appellants hereby request a one-month extension of time in order to file this Brief. Authorized fees include the statutory fee of $110 for a one-month extension of time, as well as the $320 fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 39-42 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc., (Reel 8158, Frame 0527) who is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 39-42
Claims allowed:	(none)
Claims canceled:	Claims 1-12, 14-16, and 18
Claims withdrawn:	13, 17, and 19-38
Claims on Appeal:	Claims 39-42 (Copy of claims on appeal, as amended, in attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

There were no amendments submitted after Final Rejection.

(5) SUMMARY OF THE INVENTION

The invention at issue, identified in the patent application as a human stem cell antigen, abbreviated as SCAH-2, is a polypeptide sequence encoded by a gene that is expressed in humans. The novel polypeptide is demonstrated in the specification to be a member of the class of LY-6 family of cysteine rich proteins which are expressed on the surface of lymphoid cells (Specification, page 2, lines 21-24). LY-6 proteins block secretion of interleukin 2, an approved anti-cancer agent and key regulatory hormone in cell-mediated immunity, and high expression levels of LY-6 proteins are associated with autoimmune disorders and malignancy (Specification, page 1, lines 23-27 and page 1, line 35 through page 2, line 12). SCAH-2 is 123 amino acids long and has chemical and structural homology to chicken stem cell antigen 2 (GI 509840; SEQ ID NO:20). In particular, SCAH-2 has 27% identity to chicken stem cell antigen 2 (Specification, page 6, lines 10-13). In addition, SCAH-2

conserves 6 cysteine residues characteristic of Ly-6 family proteins (Specification, page 6, lines 15-19, and Figure 3). Northern analysis shows the expression of SCAH-2 in tissues removed from bladder tumor and uterus (Specification, page 5, lines 23-25). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

(6) THE FINAL REJECTION

Claims 39-42 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement for SEQ ID NO:2, immunogenic or biologically active fragments of SEQ ID NO:2, or polypeptide variants having at least 90% sequence identity to SEQ ID NO:2.

Claim 39 stands rejected under 35 U.S.C. 102(b) as allegedly being anticipated by any of Wilkie et al (Genomics, 1993), Wray et al. (Gene, 1993), Burton (Nature, 1993), Gama et al. (Mol. Microbiol., 1992), Birkeland (Can. J. Microbiol., 1994), or Arendt et al. (Appl. Environ. Microbiol., 1994). Claim 39 recites "an immunogenic fragment comprising at least 5 contiguous amino acids of SEQ ID NO:2." The Examiner asserts that "all of the cited references provide polypeptides comprising at least 5 contiguous amino acids of SEQ ID NO:2" (Final Office Action, p. 3).

(6) ISSUES

1. Whether or not claims 39-42 satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, *i.e.*, would the Specification enable one of ordinary skill in the art to make and use the claimed sequences and fragments, *e.g.*, in toxicology testing, drug development, and the diagnosis of disease.

2. Whether or not claim 39, on appeal, is unpatentable under 35 U.S.C. §102(b) for being anticipated by any of Wilkie et al (Genomics, 1993), Wray et al. (Gene, 1993), Burton (Nature, 1993), Gama et al. (Mol. Microbiol., 1992), Birkeland (Can. J. Microbiol., 1994), or Arendt et al. (Appl. Environ. Microbiol., 1994).

(7) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

As to Issue 2

This issue pertains only to claim 39.

(8) APPELLANTS' ARGUMENTS

ISSUE 1: Enablement rejections under 35 U.S.C. § 112, first paragraph

Claims 39-42 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The Examiner has asserted that "the specification does not reasonably provide enablement for immunogenic or biologically active fragments of SEQ ID NO:2, or polypeptide variants having at least 90% sequence identity to SEQ ID NO:2" (Office Action mailed February 6, 2001, page 6).

Appellants note that the Examiner previously withdrew a 101 utility rejection of the claims "in light of the exhibits provided by the applicant" (Final Office Action, page 2), thus conceding that the claimed SCAH-2 polypeptide encodes a stem cell antigen, and that this stem cell antigen is useful. These exhibits included BLAST results of SCAH-2 against the Genpept database which showed that all of the ten hits (seven of which are pre-filing references and three of which are post-filing references) are stem cell antigens, as well as information in the specification as filed, including the disclosed homology to chicken stem cell antigen-2 (page 6, lines 10-13), the presence of conserved cysteine residues (page 6, lines 15-19), and the identification of cDNAs encoding SCAH-2 in tumor tissues (page 5, lines 23-25). In addition, a post-filing date reference by Reiter et al. was submitted to confirm that Appellants had correctly identified the claimed polypeptide as a stem cell antigen at the time of filing. This post-filing reference discloses a protein having an amino acid sequence with 99% identity to SEQ ID NO:2 (differing only at the position of the "X" residue in SEQ ID NO:2), referred to as prostate stem cell antigen (PSCA). Like the other members of the Ly-6 family, PSCA is a GPI-anchored glycoprotein expressed on the cell surface (Reiter, page 1738). PSCA is predominantly prostate-specific in normal tissues and is overexpressed in over 80% of prostate cancers (Reiter, page

1739, column 1).

The asserted utilities for the claimed polypeptides include the use of SCAH-2 in screening, diagnosis and treatment of cancers, as asserted in the specification at, for example, page 3, lines 9-14, and page 18, lines 12-17 wherein the specification states that "[s]ince a high level of expression of stem cell antigens is correlated with tumors from a variety of tissues and a more malignant phenotype, the SCAH-1 and SCAH-2 proteins can be used to identify antibodies, antagonists, and inhibitors which would diminish the efficiency of local tumor growth without inducing cell proliferation." Methods for diagnostic assays and drug screening are disclosed in the specification at, for example, pages 20-21.

Variants of SCAH-2 which retained the activity of SCAH-2 in being expressed on the surface of stem cells would clearly have the same utilities as SCAH-2 itself. An immunogenic fragment of SEQ ID NO:2 is obviously useful for producing the antibodies described above. These antibodies are useful in the diagnostic assays described at page 20, lines 5-29. Biologically and immunologically active fragments are also useful in drug screening techniques ("SCAH, its catalytic or antigenic fragments or oligopeptides, can be used for screening therapeutic compounds in any of a variety of drug screening techniques" page 20, lines 33-34). Thus there can be no doubt that the claimed variants and fragments all have utility, and that one of ordinary skill in the art would know how to use these variants and fragments without any undue experimentation.

In the Advisory Action, the Examiner asserts that "the instant specification fails to identify the entirety of SCAH-2 as the residue at position 94 is ambiguous" (Advisory Action, page 2). Appellants first note that the presence of the "X" residue at position 94 was explicitly pointed out by Appellants in the Response to Office Action filed May 7, 2001. Thus the Examiner's contention that "applicant alleged that the amino acid sequence of PSCA and SCAH-2 were identical" (Advisory Action, page 2) is not correct. Appellants clearly stated the facts at the time the reference was introduced on May 7, 2001, and the Examiner did not raise any objections in the subsequent Final Office Action mailed July 31, 2001. Moreover, the use of "X" where there is more than one possibility for the amino acid present at a specific position in the sequence is a well known convention in the art and does not render the entire sequence undisclosed.

The Examiner then asserts that "the biological function of PSCA is unknown as members of the LY-6 family exhibit diverse cellular functions" and that therefore "the only utility of SCAH-2 revealed by Reiter et al is in the diagnosis of prostate cancer" (Advisory Action, page 2). Appellants note that while the precise physiological functions of each LY-6 protein may vary, the LY-6 proteins as a family are known to block secretion of interleukin 2, an approved anti-cancer agent and key regulatory hormone in cell-mediated immunity, and high expression levels of LY-6 proteins are associated with autoimmune disorders and malignancy (Specification, page 1, lines 23-27 and page 1, line 35 through page 2, line 12). This is sufficient evidence to that one of ordinary skill in the art would reasonably believe that LY-6 family proteins such as SCAH-2 are associated with cancers and malignancy, and thus would be useful in diagnosis and treatment of such disorders. The teachings of Reiter et al that PSCA is useful in the diagnosis of prostate cancer confirms the utilities in screening, diagnosis and treatment of cancers which were asserted by the applicants at the time of filing.

The Examiner further asserts that "the instant specification fails to teach the diagnosis of prostate cancer or any other specific cancer based on the detection of SEQ ID NO:2" (Advisory Action, page 2). The Board's attention is respectfully directed to the specification at page 24, lines 14-18 ("The polynucleotides disclosed herein may be useful in the treatment of conditions associated with the tissues used to construct the cDNA libraries (shown in the Sequence ID Listing) which contained partial scah sequences. These include, but are not limited to, conditions such as leukemias and cancers of the bladder, breast, lung, ovary, prostate and uterus.") Thus the association of SCAH-2 with prostate cancer, as well as other specific cancers, was disclosed in the specification. The specification further discloses that "a high level of expression of stem cell antigens is correlated with tumors from a variety of tissues and with a more malignant phenotype" (page 18, lines 12-13). Thus, in contrast to the assertions of the Examiner (Advisory Action, paragraph bridging pages 2 and 3), the specification discloses specific diseases to be diagnosed, specific body tissues, and the expected change in expression levels associated with disease diagnosis.

In the Office Action mailed February 6, 2001, the Examiner asserted that "Given the lack of guidance in the specification for choosing which amino acid residues of SEQ ID NO:2 will tolerate

substitution, either separately or in groups, and which specific amino acids can be substituted in at any specified location, one of skill in the art would be forced into undue experimentation without reasonable expectation of success in order to practice the claimed invention" (Office Action mailed February 6, 2001, pages 7-8). In support of this assertion, the Examiner cited references that gave examples where single amino acid changes altered the function of a protein. These references are not relevant to the instant case, because the claims specify "an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:2, wherein said amino acid sequence is expressed on the surface of stem cells." Only variants which retain this activity are claimed, not all possible variants. One of skill in the art need only test whether a naturally occuring variant, which can be identified through methods well known in the art and described in the specification (at, for example, page 22, lines 1-7) has the required activity. Assays for determining the presence and distribution of SCAH-2 molecules in cell populations are described in the specification at, for example, page 38, lines 10-12. The specification has also disclosed residues which are conserved across a number of stem cell antigens and thus likely to be important for function, for example, the conserved cysteine residues (see the specification at page 6, lines 15-19). Thus the skilled artisan would have additional guidance in making and using the claimed variants.

With respect to the claimed biologically active fragments, the Examiner has asserted that "one of skill in the art could not anticipate what amino acid sequence(s) would retain the function of the SCAH-2 polypeptide" and cited references pertaining to the three-dimensional structures of proteins (Office Action mailed February 6, 2001, page 8). Once again, these references are not relevant as the claims recite "a biologically-active fragment of the amino acid sequence of SEQ ID NO:2, wherein said biologically-active fragment is expressed on the surface of stem cells," an activity for which the specification has provided assays. It is not necessary for the specification to list the sequences of all the biological fragments encompassed by the claims, since one of ordinary skill in the art would be able to identify and use those biologically active fragments retaining the required activity by following the guidance in the specification, without any undue experimentation.

The Examiner asserts that the expression of SCAH-2 on the surface of stem cells does not

suffice to enable SCAH-2, as "the specification does not teach a specific type of stem cell in terms of identifying the cell lineage(s) which arises from said stem cell, or the organ or tissue arising from the proliferation of said stem cells" (Advisory Action, page 3). Appellants note that the specification does identify specific tissues in which scah sequences were found to be expressed, including bladder, breast, lung, ovary, prostate and uterus (page 24, lines 14-18). Thus one of ordinary skill in the art would be able to determine the bodily tissues from which to isolate the stem cells without any undue experimentation.

With respect to the claimed immunologically active fragments, the Examiner has asserted that the specification does not teach any examples of immunologically active fragments. The Examiner further asserted that "[t]he determination of an immunogenic fragment is clearly a non-trivial enterprise, and without further guidance from the specification on known sequences of the SEQ ID NO:2 polypeptide which have been determined to be immunogenic fragments in a specific organism, it would require undue experimentation for one of skill in the art to make and use the invention as claimed" (Office Action mailed February 6, 2001, page10).

Appellants respectfully point out that the generation of antibodies to proteins is well known in the art and is routinely successful without knowledge of the crystal structure of the protein, in contrast to the assertions of the Examiner. In addition, the specification provides further guidance as to the selection of immunogenic fragments. See, for example, page 38, lines 15-21, wherein the specification describes software programs used to determine regions of high immunogenicity and also discloses that appropriate epitopes may include "those near the C-terminus or in hydrophilic regions." A hydrophobicity plot for SCAH-2 is provided in Figure 5. Appellants note that Paul et al., a reference cited by the Examiner, concurs that "hydrophilicity has been proposed as a second indication of immunogenicity" and that of 12 proteins tested, "the most hydrophilic site of each protein was indeed one of the antigenic sites" (Paul et al., page 249). Thus even the evidence cited by the Examiner confirms that based upon the guidance provided in the specification, one of ordinary skill in the art would be able to make and use immunogenic fragments of SEQ ID NO:2 without any undue experimentation.

ISSUE 2: Rejections under 35 U.S.C. § 102

The Examiner has asserted that claim 39(d) is anticipated by any of Wilkie et al (Genomics, 1993), Wray et al. (Gene, 1993), Burton (Nature, 1993), Gama et al. (Mol. Microbiol., 1992), Birkeland (Can. J. Microbiol., 1994), or Arendt et al. (Appl. Environ. Microbiol., 1994). Claim 39 recites "an immunogenic fragment comprising at least 5 contiguous amino acids of SEQ ID NO:2." The Examiner asserts that "all of the cited references provide polypeptides comprising at least 5 contiguous amino acids of SEQ ID NO:2" (Final Office Action, page 3), and in particular, that the Wilkie, Wray, Gama, and Arendt references teach a polypeptide comprising 8 contiguous amino acids of SEQ ID NO:2, while the Burton and Birkeland references each teach a polypeptide comprising 7 contiguous amino acids of SEQ ID NO:2 (Advisory Action, page 3).

This is simply incorrect. Appellants have previously submitted sequence alignments using the CLUSTALW algorithm between SEQ ID NO:2 and the polypeptides of Wray et al., Burton, Wilkie et al,. and Birkeland (Exhibit A, submitted with Response to Final Office Action). It was not possible to perform alignments for the other two references because it could not be determined which of over 40 possible proteins was referred to in the case of Gama et al., and because no protein sequences were found in the GenBank database associated with the Arendt et al publication.

It can be plainly seen from these alignments that there is no region of greater than 4 contiguous amino acids that is shared by SEQ ID NO:2 and any of the reference polypeptides. See, for example, the alignment between SEQ ID NO:2 and the sequence of Wilkie et al., in which the longest contiguous shared sequence is LALL, from L6 to L9 of SEQ ID NO:2. Appellants note that these regions are too short for use as immunogenic peptides. The experiments described in Paul et al., for example, used peptides from 6 to 14 residues long (Paul et al., p. 250). Appellants further note that the Examiner has not submitted any sequence alignments to provide evidence for her claim that the references all provide polypeptides comprising at least 5 contiguous amino acids of SEQ ID NO:2. In the absence of any such evidence, and the presence of clear and convincing evidence from Appellants that the reference polypeptides do not comprise the claimed fragments, the Examiner must conclude that these reference polypeptides do not anticipate the claims.

Accordingly, reversal of the rejections under 35 U.S.C. § 102 is requested.

(9) CONCLUSION

For all of the above reasons, it is urged that the decision of the Examiner rejecting claims 39-42, on appeal, is in error and should be reversed.

Respectfully submitted,

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Date: April 10, 2002

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APPENDIX

Claims on Appeal:

39. A purified polypeptide comprising an amino acid sequence selected from the group consisting of:

a) an amino acid sequence of SEQ ID NO:2,

b) an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:2, wherein said amino acid sequence is expressed on the surface of stem cells,

c) a biologically-active fragment of the amino acid sequence of SEQ ID NO:2, wherein said biologically-active fragment is expressed on the surface of stem cells, and

d) an immunogenic fragment of the amino acid sequence of SEQ ID NO:2, wherein said immunogenic fragment comprises at least 5 contiguous amino acids of SEQ ID NO:2 and is capable of generating an antibody that specifically binds to the polypeptide encoded by SEQ ID NO:2.

40. An isolated polypeptide of claim 39, having a sequence as depicted in SEQ ID NO:2.

41. A pharmaceutical composition comprising an effective amount of a polypeptide of claim 39 and a pharmaceutically acceptable excipient.

42. A pharmaceutical composition comprising an effective amount of a polypeptide of claim 40 and a pharmaceutically acceptable excipient.